II. REMARKS/ARGUMENTS

A. Status of the Claims

New claims 65-70 have been added.

Claims 38, 47, 54, 55, 57, and 61 were amended without prejudice or admission.

Support for an oral dosage form "consisting essentially of (a) two analgesic compounds and/or pharmaceutically acceptable salts thereof consisting of (i) meloxicam and/or at least one pharmaceutically acceptable salt thereof and (ii) oxycodone and/or at least one pharmaceutically acceptable salt thereof; and (b) a sustained release carrier" in claims 38 and 55 can be found, e.g., on page 11, lines 1-6, of the specification, and on page 7, lines 21-25, of Application Serial No. 60/059,195 ("the '195 application") to which the present application claims priority to ("... the invention comprises an oral solid dosage form comprising ... an opioid analgesic together with .... a COX-2 inhibitor [and optionally] a sustained release carrier which causes the sustained release of the opioid analgesic, or both the opioid analgesic and the COX-2 inhibitor."). Oxycodone is an opioid analgesic. See, e.g., page 10, lines 19-21, of the '195 application ("... the opioid analgesic is selected from ... oxycodone ..."). Meloxicam is a COX-2 inhibitor. See, e.g., page 9, lines 22-25 ("... COX-2 inhibitors include ... meloxicam ...").

Support for "the sustained release carrier ... in an amount which causes a sustained release of (i) the meloxicam and[/or] (ii) the oxycodone when the dosage form contacts gastrointestinal fluid" in claims 38, 65 and 68 can be found, e.g., on page 7, lines 21-25, of the specification and on page 19, lines 8-9, of the '195 application ("... the invention comprises an oral solid dosage form comprising ... an opioid analgesic together with .... a COX-2 inhibitor [and optionally] a sustained release carrier which causes the sustained release of the opioid analgesic, or both the opioid analgesic and the COX-2 inhibitor.").

Support for "the sustained release carrier in an amount which causes a sustained release of the oxycodone for about 8 to 24 hours when the dosage form contacts gastrointestinal fluid" in claims 55, 66 and 69 and for "sustained release of said oxycodone for about 24 hours" in claim 66 can be found, e.g., on page 38, line 31, of the specification and page 37, lines 16-17, of the '195 application ("... provides sustained release of the therapeutically active agent for a time period of from about 8 to about 24 hours").

Support for "the oral dosage form administered twice-a-day" in claims 67 and 70 can be found, e.g., on page 20, line 31, of the specification, and on page 13, lines 23-25, of the '195 application. ("A composition comprising [a combination] ... of opioid analgesics and COX-2 inhibitors may be administered in divided doses ranges from 2 to 6 times per day ....").

Support for the "low back and neck pain" in claims 54 and 57 can be found, e.g., on page 22, line 12 of the specification, and on page 15, line 20, of the '195 application ("... low back pain and neck pain...").

Support for "combining (i) meloxicam or a pharmaceutically acceptable salt thereof, (ii) a sustained release material and (iii) oxycodone or a pharmaceutically acceptable salt thereof into an oral dosage form" in claim 65 can be found, e.g., on page 18, lines 21-23, of the specification, and page 11, lines 11-22, of the '195 application. ("[t]he amount of COX-2 inhibitor that may be combined with the carrier materials to produce a single dosage form having COX-2 in inhibitor in combination ....").

Applicants respectfully submit that no new matter has been added by virtue of the present amendments.

Claims 38, 47 and 53-70 are now pending and are encompassed by the elected invention, including the elected species.

B. Substance of Interview

Applicants hereby make of record the substance of the telephone interview conducted on February 17, 2011, between the undersigned attorney and Examiner Christopher M. Gross.

During the interview, potential claims amendments for overcoming the obviousness rejections and further differentiating over the cited references were discussed. In particular, the replacement of the term "comprising" immediately following the preamble of clams 38 and 55 with the term "consisting" and the replacement of the term "comprising" on line 3 of claims 38 and 55 with the term "consisting essentially of" were discussed. It was suggested such amendments may overcome the present obviousness rejections, because such an amendment will exclude a possibility of utilizing the compound of formula (I) of Iyengar et al. in the methods of present claims 38 and 55. Claims 38 and 55 have therefore been amended in the present response to (i) replace the term "comprising" immediately following the preamble of clams 38 and 55 with the term "consisting" and (ii) to replace the term "comprising" on line 3 of claims 35 and 55 with the term "consisting essentially of."

With respect to the purported motivation for replacing ibuprofen with meloxicam in the compositions of the Baker reference and secondary considerations of non-obviousness, a possibility of submitting a reference showing that ibuprofen was associated with a lower risk of gastrointestinal reactions than the agents the tolerability of which was compared to meloxicam in the Furst article (i.e., naproxen, diclofenac and piroxicam) was discussed. A copy of Pharmacovigilance August 1994 article stating, e.g., that "Ibuprofen was associated with the lowest risk [of upper gastrointestinal reactions] in all studies in which it was included," as compared to, e.g., naproxen, diclofenac and piroxicam), is being submitted concurrently herewith as Appendix A, and This teaching is discussed in more detail in response to the obviousness rejections below.

Applicants thank the Examiner for the telephone interview and respectfully request that the substance of this interview be made of record.

C. Information Disclosure Statement

The Examiner states on page 2 of the Office Action that the Information Disclosure Statement filed on April 26, 2010, was "placed in the application file, but the information referred to therein regarding citation A05 (Lichtblau et al), has not been considered since the copy provided to the office is not readable."

A copy of the Lichtblau citation was re-submitted with the Information Disclosure Statement filed on February 23, 2011. Applicants respectfully request that in the interests of compact prosecution the Examiner calls the undersigned attorney before the issuance of the next Office Action in the event that there are any issues with the readability of the re-submitted citation.

It is Applicants' understanding that citations A01, A02, A04 and A06 of the Information Disclosure Statement filed on April 26, 2010, were considered by the Examiner, as indicated on the Form PTO-1449 attached to the present Office Action; and that citations A03 and A07 of the Information Disclosure Statement filed on April 26, 2010, were previously considered by the Examiner, as indicated on PTO-892 of August 26, 2004 and PTO-892 of November 30, 2006. If Applicants' understanding is incorrect, the Examiner is respectfully invited to call the undersigned attorney before the issuance of the next Office Action, so that a supplemental Information Disclosure Statement re-submitting these citations can be prepared and timely filed.

D. Claim Rejections- 35 U.S.C. § 103

1. Baker et al. (U.S. Patent No. 4,569,937) in view of the Furst article,Oshlack I et al. (U.S. Patent No. 5,472,712), Oshlack II (U.S. Patent No. 6,294,195) and Iyengar et al. (WO 97/25988)

Claims 38, 47, 48, 53, and 54 were rejected under 35 U.S.C. § 103(a) over Baker et al. (U.S. Patent No. 4,569,937) in view of Furst (Furst, D.E. "Meloxicam: Selective COX-2 inhibition in clinical practice" Seminars in Arthritis and Rheumatism, June 1997, 26(1), 21-27) and in further view of Oshlack I et al. (U.S. Patent No. 5,472,712) and/or Oshlack II (U.S. Patent No. 6,294,195) and Iyengar et al. (WO 97/25988).

The rejection is respectfully traversed for the reasons presented in the response filed on March 24, 2010, hereby incorporated by reference, and the reasons given below.

The Examiner states on page 4 of the Office Action that "Baker et al. fails to disclose compositions with Meloxicam." Based on the disclosure of the Furst article, the Examiner takes a position that "a person of skill in the art would have been motivated to use Meloxicam ... because it is safer than other NSAIDs including the ibuprofen disclosed by Baker et al." Office Action, page 6.

Applicants respectfully disagree with the Examiner's position. The Furst article compared the GI toxicity of meloxicam with the GI toxicity of naproxen, diclofenac and piroxicam, rather than ibuprofen. See, e.g., Abstract ("[a] global safety analysis of clinical trials, representing over 5,600 patients and comprising 170 and 1,100 patient-years of exposure for meloxicam caused less GI toxicity and fewer peptic ulcers and GI bleeds than naproxen, diclofenac, or piroxicam."). The Furst article did not compare GI toxicity of ibuprofen with the GI toxicity of meloxicam, and did not make any conclusions about comparative safety of ibuprofen and meloxicam.

Applicants respectfully submit that on the filing date of the present application, it was inappropriate to conclude that an agent that inhibits COX-2 to a greater extent than COX-1 (e.g., meloxicam), would necessarily be associated with a lower incidence of gastrointestinal side effects than an agent that is less COX-2 selective (e.g., ibuprofen). In fact, at the filing date of the present application, it was known that certain agents that are more COX-2 selective than ibuprofen were associated with a higher risk of gastrointestinal complications than ibuprofen, as evidenced, for example, by the Pharmacovigilance article of August 1994, a copy of which is attached as Appendix A to the present response.

According to the Pharmacovigilance article, in 1994, "Ibuprofen was associated with the **lowest** risk [of upper gastrointestinal reactions for individual non-aspirin NSAD's] in all studies in which it was included," including, e.g., naproxen, diclofenac and piroxicam described in the Furst article. See, e.g., Pharmacovigilance August 1994, page 9, the penultimate paragraph in column 1; see also Figure 1, Figure 2, Figure 3, and Figure 5 (emphasis added). "Diclofenac, naproxen and indomethacin were associated with risks which **are clearly higher** than those for ibuprofen." Id. (emphasis added).

According to the Furst article, diclofenac and indomethacin are **more** COX-2 selective than ibuprofen in human whole blood assays. See, e.g., Table I of the Furst article showing IC_{50} COX-2/COX-1 ratio of 0.33 for diclofenac, IC_{50} COX-2/COX-1 ratio of 3.0 for indomethacin, and IC_{50} COX-2/COX-1 ratio of 4.6 for ibuprofen, and stating that higher IC_{50} COX-2/COX-1 ratio "values denote less COX-2 selectivity."

In other words, according to the Pharmacovigilance article, diclofenac and indomethacin, NSAIDs which are more COX-2 selective than ibuprofen, are associated with risks of gastrointestinal complications "which **are clearly higher** than those for ibuprofen." See, e.g., Pharmacovigilance August 1994, page 9, the penultimate paragraph in column 1; see also Figure 1, Figure 2, Figure 3, and Figure 5 (emphasis added). Therefore, on the filing date of the present application, it was not reasonable to conclude that an agent that inhibits COX-2 to a greater

extent than COX-1 (e.g., meloxicam), would necessarily be associated with a lower incidence of gastrointestinal side effects than an agent that is less COX-2 selective (e.g., ibuprofen).

For the same reason, it was not reasonable to predict that substituting ibuprofen for meloxicam in the compositions according to Baker et al. would provide an analgesic "with fewer gastrointestinal side-effects" than ibuprofen, as asserted by the Examiner on page 12 of the Office Action, e.g., because the Pharmacovigilance August 1994 article states that "Ibuprofen was associated with the **lowest** risk [of upper gastrointestinal reactions for individual non-aspirin NSAD's] in all studies in which it was included."

The combination of the cited references would not therefore have suggested to or motivated the skilled person to modify the compositions of Baker by replacing ibuprofen with meloxicam, especially in view of the fact that the Pharmacovigilance August 1994 article stated that "Ibuprofen was associated with the **lowest** risk [of upper gastrointestinal reactions for individual non-aspirin NSAD's] in all studies in which it was included."

Applicants respectfully reiterate that the combination of the cited references does not provide any suggestion or motivation for the skilled person to modify the compositions of Baker by replacing ibuprofen with meloxicam. There is nothing in the Baker reference (or any other cited reference) that mentions the gastrointestinal toxicity of the ibuprofen compositions described therein. As stated above, the Furst article does not compare GI toxicity of ibuprofen with the GI toxicity of meloxicam, and does not make any conclusions about comparative safety of ibuprofen and meloxicam. In view of the Pharmacovigilance August 1994 article, it would not have been concluded from the Furst article that meloxicam was expected to have a lower GI toxicity than ibuprofen. Furthermore, the skilled person would not have been motivated by any of the cited references to modify the compositions of Baker by replacing ibuprofen with meloxicam.

With respect to secondary considerations of non-obviousness, Applicants respectfully note that more than 26 years later after the filing date of the Baker reference, there is no approved product on the market comprising oxycodone and meloxicam.

In an effort to advance prosecution and further differentiate over the cited references, independent claim 38 has been amended herein to replace the term "comprising" immediately following the preamble of the claim with the term "consisting of" and the term "comprising" on line 3 of the claim with the term "consisting essentially of." Amended independent claim 38 is directed to a method of effectively treating pain in humans "**consisting of** orally administering to a human patient an oral dosage form consisting essentially of two analgesic compounds consisting of ... (i) meloxicam ... and (ii) oxycodone ...."

This amendment to claim 38 excludes the possibility of compounds of Formula I of Iyengar et al. being utilized in the method of claim 38. The phrase "consisting essentially of" precludes the presence of an active agent other than meloxicam and oxycodone (i.e., a compound of Formula I of Iyengar et al.) in the dosage form recited in claim 38 because the present specification makes it clear (e.g., on page 1, lines 7-10), that the invention "relates to analgesic pharmaceutical compositions containing an opioid analgesic and a cylooxygenase-2 (COX-2) inhibitor" and "methods of treating pain comprising administering such pharmaceutical compositions to humans;" and does <u>not</u> mention compounds of Formula I of Iyengar et al..

Applicants respectfully submit that the combination of the cited references does not render a method of treating pain without the use of the compounds of Formula I of Iyenger et al. as recited in claim 38 obvious, because the method of claim 38 as amended herein excludes an essential component of one of the cited references (i.e., the compound of Formula I of Iyenger at al.). Oxycodone and meloxicam have structures that are different and not encompassed by the structure of the compound of Formula I of Iyenger. See, e.g., pages 3-4 of Iyenger for the structure of the compound of Formula I, and page 46 for the structure of oxycodone.

Further, Iyenger et al. describes compounds of Formula I as tachykinin receptor antagonists. See, e.g., pages 2 and 31-33.

Oxycodone exhibits its analgesic effects through activation of μ and κ opioid receptors, and meloxicam is believed to exhibit its analgesic effect through inhibition of COX enzymes. There is nothing in the cited references that would have suggested that oxycodone and meloxicam have any affinity to tachykinin receptors or might act as antagonists at the tachykinin receptors.

The combination of the cited references cannot render the method of claim 38 obvious, as it is believed that the purported modification will change the principle of operation of the Iyenger et al.. See, e.g., MPEP, section 2143.01 (VI) ("The proposed modification cannot change the principle of operation of a reference.").

Applicants further submit that there is no description in the cited references to combine meloxicam, oxycodone and a sustained release material into a dosage form. Therefore, the combination of the cited references does not teach or suggest a dosage form consisting essentially of meloxicam, oxycodone and a sustained release material as recited in claim 38.

Applicants moreover submit that none of the cited reference describes administration of meloxicam in combination with oxycodone as recited in claim 38, and therefore they do not teach or suggest the method of claim 38.

In response to the Examiner's reliance on MPEP 2144.06 and In re Kerkhoven on page 8 of the Office Action and on In re Diamond and Kellman on page 9 of the Office Action, Applicants respectfully note that the present rejection involves the destruction and modification of the compositions described in the primary reference, rather than merely "combine[s] two compositions" to form a third composition as was purportedly done in the cases cited by the Examiner. Applicants therefore submit that the Examiner's reliance on these cases is misplaced.

Applicants respectfully reiterate that at the time of filing of the present application, meloxicam was not considered an equivalent of ibuprofen. In fact, none of the cited references even lists ibuprofen and meloxicam in the same Markush group.

For the foregoing reasons, withdrawal of the rejection is respectfully requested.

2. **Baker et al. (U.S. Patent No. 4,569,937) in view of Furst article,Oshlack I, Oshlack II and Iyengar, Eichel et al. (U.S. Patent No. 5,376,384) and Miller et al. (EP 0649657)**

Claims 38, 47, 48, and 53-64 were rejected under 35 U.S.C. § 103(a) over Baker, Furst, Oshlack I, Oshlack II, Iyengar et al., Eichel et al. (U.S. Patent No. 5,376,384) and Miller et al. (EP 0649657). The Eichel and Miller references were relied upon by the Examiner for the purported teaching of an immediate-release form used in conjunction with a sustained release form.

The rejection is respectfully traversed, for the reasons presented in the response filed on March 24, 2010, hereby incorporated by reference, and the for the additional reasons given below.

Applicants respectfully submit that the combination of the cited references does not provide suggestion/motivation to the skilled person to modify the compositions of Baker by replacing ibuprofen with meloxicam for the reasons given above in response to the first obviousness rejection.

In an effort to advance prosecution and further differentiate over the cited references, independent claims 38 and 55 have been amended herein. Amended claims 38 and 55 are each directed in part to a method of effectively treating pain in humans "**consisting of** orally

administering to a human patient an oral dosage form consisting essentially of two analgesic compounds consisting of ... (i) meloxicam ... and (ii) oxycodone ...."

As stated above, this amendment excludes the possibility of compounds of Formula I of Iyengar et al. being utilized in the methods of claims 38 and 55 or being present in the dosage forms of claims 38 and 55.

For the reasons given above, the combination of the cited references does not teach or suggest a method of treating pain by excluding the compounds of Formula I of Iyenger et al., as now recited in claims 38 and 55.

With further regard to claim 55, Applicants respectfully submit that the dosage form recited in claim 55 includes two different agents in two different forms- oxycodone in a sustained release and meloxicam in an immediate release form.

The combination of the cited references does not describe a dosage form which includes oxycodone in a sustained release form and meloxicam in an immediate release form. With respect to the Examiner's reliance on page 13, column 3, lines 10-24, of Eichel et al., Applicants respectfully note that Eichel et al. does not mention meloxicam and that the portion of the reference relied upon by the Examiner refers to a multi-layered tablet comprising the **same** drug (i.e., acetaminophen) in both a sustained release form and an immediate release form, rather than two different agents in two different forms as recited in instant claim 55. Similarly, Eichel et al., column 3, lines 25-39, and column 5, lines 7-11, also does not render obvious a dosage form which includes two different drugs in two different forms as recited in claim 55.

With respect the Examiner's reference to column 6, lines 37-48, of Miller et al., Applicants submit that, given the fact that Miller et al. does not mention meloxicam, the general statement in Miller et al. that the unit dosage form "may be formulated to give immediate release of the active ingredients upon administration or may be adapted to give delayed or sustained

release or, indeed, a combination of both immediate and delayed or sustained release" is insufficient to provide motivation to formulate a dosage form which includes "oxycodone in a sustained release form and meloxicam in an immediate release form" as recited in claim 55.

Applicants respectfully reiterate that none of the cited references describes administration of meloxicam in combination with oxycodone as recited in claims 38 and 55, or a dosage form consisting essentially of meloxicam, oxycodone and a sustained release carrier as recited in claims 38 and 55. Therefore, no combination of the cited references renders the methods of claim 38 and 55 obvious.

With further regard to claims 63 and 64, Applicants submit that the combination of the cited references does not teach or suggest administering meloxicam twice a day, at the very least because the reference relied upon for the teaching of meloxicam (i.e., the Furst reference) describes administration of meloxicam once a day. Applicants therefore submit that, for this additional reason, the combination of the cited references does not render claims 63 and 64 obvious. In response to the Examiner's reference to claim 3 of Miller et al. on page 15 of the Office Action, Applicants respectfully note that Miller et al. does not mention meloxicam, and therefore cannot teach or suggest that meloxicam is suitable for twice-a-day administration.

For the foregoing reasons, withdrawal of the rejection is respectfully requested.

E. Rejection under 35 U.S.C. § 112

Claims 54 and 57 were rejected, allegedly for failing to comply with the written description requirement for reciting the phrase "low back pain **or** neck pain."

In an effort to advance prosecution, claims 54 and 54 were each amended to replace the phrase "low back pain **or** neck pain" with the phrase "low back pain **and** neck pain." As

acknowledged by the Examiner on page 17 of the Office Action, the phrase "low back pain **and** neck pain" is literally supported on page 22, line 13, of the specification.

Withdrawal of the rejection is respectfully requested.

III. CONCLUSION

An early and favorable action on the merits is earnestly solicited. The Examiner is respectfully requested to contact the undersigned at the telephone number provided below in the event that a telephonic interview will advance the prosecution of the application.

Respectfully submitted,
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APPENDIX A

COMMITTEE ON SAFETY OF MEDICINES

CURRENT PROBLEMS in Pharmacovigilance

MEDICINES CONTROL AGENCY

IN THIS ISSUE: Page No.

Relative safety of oral non-aspirin NSAIDs

Recent evidence on the relative safety of 7 oral NSAIDs indicates that there are differences in the risks of serious upper gastrointestinal adverse reactions. Doctors should take account of these differences when prescribing NSAIDs.

Introduction

Treatment with non-aspirin NSAIDs is associated with a variety of serious adverse reactions. Most commonly these involve the upper gastrointestinal tract, including peptic ulceration and its complications of perforation and bleeding. Other serious reactions, such as those involving the kidney and liver, blood disorders and allergy (e.g. anaphylaxis) are less common but they are also important. Based on UK spontaneous ADRs, our previous review in 1986[1,2] made recommendations for the safer use of NSAIDs. This article extends that review and offers further advice to prescribers.

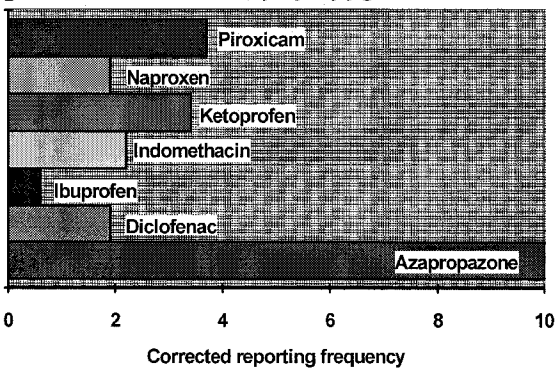
Upper gastrointestinal toxicity

Ten epidemiological studies[3-12] have now provided information on the risks of upper gastrointestinal reactions for individual non-aspirin NSAIDs. Such evidence is not available for all the oral NSAIDs marketed in the UK but does include those used most widely. Although estimates of the magnitude of increased risk vary between studies, there is some consistency in the rank order of risk for individual drugs.

Ibuprofen was associated with the lowest risk in all studies[3,4,8-12] in which it was included. Diclofenac[4,6-12], naproxen[3-5,7-12] and indomethacin[3-12] were associated with risks which are clearly higher than those for ibuprofen. There was some variation in the risks for ketoprofen[8,10-12] but, overall, it seems comparable with other drugs associated with intermediate risk. Piroxicam was included in 9 studies[4-12] and was associated with the highest risk in three[4,9,10] and the second highest in four[5,7,8,11]. Azapropazone was included in 2 studies[11,12] and in each was associated with the highest risk.

Yellow card reporting frequencies for gastrointestinal reactions over the last 5 years are shown in figure 1. These have been corrected for annual trends in reporting and are expressed as reports per 100,000 prescriptions. Azapropazone was associated with the highest reporting frequency followed by piroxicam and ketoprofen. Lower reporting frequencies were observed with diclofenac, naproxen and indomethacin. Ibuprofen was associated with the lowest reporting frequency.

Figure 1 - GI reactions (1989-1993)



Thus there is broad consistency between epidemiological studies and the yellow card database in the rank order of NSAIDs associated with serious upper gastrointestinal toxicity.

Other adverse reactions

Spontaneous reporting of other reactions indicates potential differences, with azapropazone being associated with the highest reporting frequencies for renal, hepatic, allergic and haematological reactions (figures 2-5). Corrected reporting frequencies for these reactions have been calculated as described above but these data cover the last 14 years.

Figure 2 - Renal reactions (1980-1993)

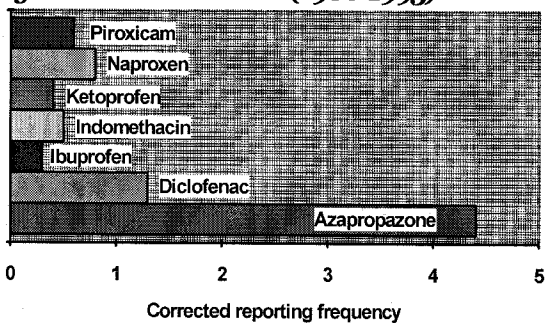


Figure 3 - Hepatic reactions (1980-1993)

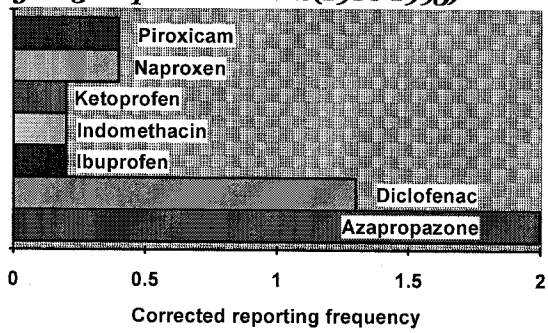


Figure 4 - Hypersensitivity reactions (1980-1993)

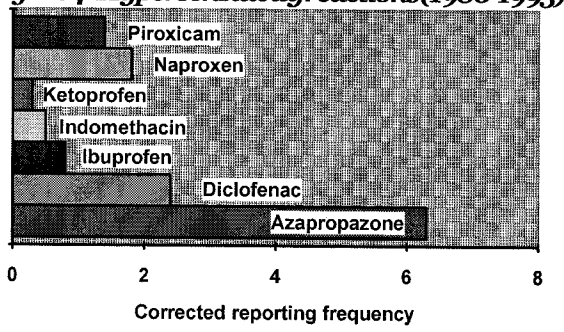
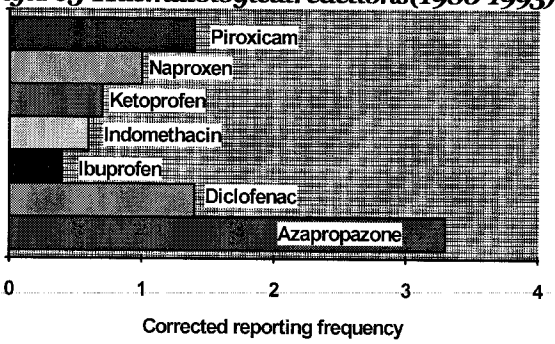


Figure 5 - Haematological reactions (1980-1993)



Yellow card data suggest possible differences between NSAIDs in respect of these rare reactions. However, few epidemiological studies have investigated the non-gastrointestinal adverse reactions to NSAIDs.

Discussion

Epidemiological studies and spontaneous ADR reports both suggest that there are important differences in the risk of serious gastrointestinal reactions between seven commonly used NSAIDs. Because the studies were observational, differences in toxicity should be interpreted with caution. Most took account of various factors which could be alternative explanations for the differences observed e.g. age, sex, past history of peptic ulcer, smoking and alcohol consumption. It should be noted that the low risks associated with ibuprofen are based largely on data relating to prescription usage.

Interpretation of comparative spontaneous ADR reporting also requires caution as substantial biases can exist. However, the findings are consistent with those of formal studies. Azapropazone was associated with the highest risk of gastrointestinal reactions in both epidemiological studies and an analysis of yellow card data. The latter also suggests that azapropazone is associated with relatively high frequencies of renal, hepatic, allergic and haematological reactions.

Gastrointestinal adverse reactions to NSAIDs have been consistently shown to be dose-related. None of the studies was able to determine whether differences in the risk of gastro-intestinal reactions observed with individual NSAIDs are explained by differences in the doses used of individual drugs. It is therefore unclear whether intrinsic differences in toxicity exist which are independent of dose. With azapropazone, over half of all UK prescriptions for azapropazone are at doses of 1200mg per day or more. It appears that some patients over 60 years are being prescribed doses which exceed those recommended in this age group. However, even when dose was taken into account in the analysis of spontaneous ADRs, marked differences remained in the reporting frequency of gastrointestinal reactions for azapropazone compared with other NSAIDs. One-fifth of prescriptions for azapropazone are for gout and although the disease itself does not appear to predispose to gastrointestinal adverse reactions, high-dose, intermittent treatment with azapropazone could do so.

Conclusions

- Observational studies and yellow card data provide evidence for differences in the risk of gastrointestinal reactions for 7 NSAIDs.
- Azapropazone is associated with the highest risk and ibuprofen the lowest.
- Piroxicam, ketoprofen, indomethacin, naproxen and diclofenac are associated with intermediate risks. Piroxicam may be associated with higher risks than other NSAIDs in this group.
- There are insufficient data to reach clear conclusions on the relative toxicity of other available oral NSAIDs.

Recommendations

Azapropazone:

- Should be restricted to use in rheumatoid arthritis, ankylosing spondylitis and acute gout and **only** used when other NSAIDs have been tried and have failed.
- Is contra-indicated in patients with a past history of peptic ulceration.
- For patients over 60 years, the maximum daily dose for the treatment of rheumatoid arthritis and ankylosing spondylitis should be restricted to 600mg.

In order to reduce the risks of adverse reactions to oral NSAIDs:

- Drugs associated with low risk should generally be preferred.
- Start at the lowest recommended dose.
- Do not use more than one oral NSAID concurrently.
- Remember that all NSAIDs are contra-indicated in patients with peptic ulceration.

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Severe cystitis with tiaprofenic acid (Surgam)

Stop treatment immediately if patients develop frequency, urgency, dysuria or haematuria

The non-steroidal anti-inflammatory drug tiaprofenic acid (Surgam) can cause bladder irritation and cystitis[1,2]. This reaction appears to be under-recognised. We have received 69 reports of cystitis associated with tiaprofenic acid, and a further 32 reports describing related urinary tract symptoms including frequency, dysuria and haematuria since the drug was introduced to the UK in 1982. Only 8 cases of cystitis have been reported for all other NSAIDs combined. Similar experience has been observed in Australia[2,3].

The duration of treatment with tiaprofenic acid before the onset of urinary tract symptoms varied considerably. Patients whose symptoms occurred within one month of starting treatment usually recovered rapidly if the drug was withdrawn. However, most patients were continued on long-term treatment and underwent extensive investigations to determine the cause of their symptoms. On cystoscopy and biopsy, the findings were often similar to idiopathic interstitial cystitis. The majority of patients with cystitis recovered after withdrawal of tiaprofenic acid but a drug-induced cause was not invariably suspected and some underwent surgical procedures. Four patients had cystectomies and two had a urinary diversion performed. **It is important that cystitis induced by tiaprofenic acid is not confused with idiopathic interstitial cystitis, as this could lead to inappropriate treatment.**

We recommend that:

- Tiaprofenic acid should **not** be given to patients with pre-existing urinary tract disorders.
- Patients should be advised to stop taking tiaprofenic acid and to report to their doctor promptly if they develop urinary tract symptoms such as increased frequency, nocturia, urgency, pain on urinating or blood in their urine.
- **If urinary tract symptoms develop, tiaprofenic acid should be stopped.**

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Adverse drug reaction reporting: Important for patient safety

Support from doctors is vital

Over the 30 years since the yellow card scheme started there has been a steady increase in the number of reports received from around 5,000 in the 1960s to 10,000 in 1980 and 20,000 in 1992. Reports are received from general practitioners, hospital doctors, coroners and dentists. The effectiveness of the scheme in identifying important drug safety hazards has been demonstrated many times[1], some recent examples are shown in Table 1. Similar schemes have been developed elsewhere in the world but few have attained the level of support from doctors that has been achieved in the UK. It is vital for patient safety that this is maintained.

Table 1: Important early warnings of new adverse reactions identified through the UK spontaneous ADR reporting scheme since 1990.

Year	Product	Adverse reaction
1990	dinoprostone (Propess)	uterine hypertonus and foetal distress
1990	phenol (Chloraseptic throat spray)	oedema of epiglottis and larynx
1990	metipranolol eye-drops (Glauline)	uveitis
1990	mesalazine (Asacol)	nephrotoxicity
1991	terodiline (Micturin)	ventricular arrhythmias
1992	terbinafine (Lamisil□)	taste loss, hepatic dysfunction
1993	paroxetine (Seroxat□)	withdrawal symptoms, dystonic reactions
1993	remoxipride (Roxiam□)	aplastic anaemia
1993	high lipase pancreatins Creon 25000□ Nutrizym 22□ Pancrease HL□ Panzytrat 25000□	colonic strictures in children with cystic fibrosis

There is bound to be some fluctuation in the number of reports submitted, and from time-to-time there have been transient falls. In 1993 there was a drop of about 2,000 compared to 1992 which, we hope, is only temporary. We recognise that the pressures on doctors are ever-increasing and that this may be a deterrent to activities such as completing a yellow card. Nevertheless, we would like to emphasise that the purpose of the scheme is to protect patients, and that it is dependent on goodwill and co-operation from all doctors. **Please continue to give it your support.**

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Fluvoxamine increases plasma theophylline levels

Concomitant use is best avoided

Theophylline is known to interact with many other widely-used drugs. A recent study[1] found that plasma theophylline levels were raised by three-fold following concomitant administration of fluvoxamine (Faverin), a selective serotonin re-uptake inhibitor (SSRI) and theophylline. The mechanism appears to be inhibition of hepatic metabolism of theophylline. To date, the interaction has not been reported for any other SSRIs.

This interaction has been reported in four published cases[2] and identified as a possible reaction on five yellow cards. Symptoms included nausea, vomiting, headache and agitation.

Concomitant use of fluvoxamine and theophylline or aminophylline preparations should usually be avoided. Where this is not possible, patients taking this combination should have their theophylline dose halved and plasma theophylline levels monitored closely.

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